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AHRQ's Comparative Effectiveness Research on Premixed Insulin Analogues for Adults with Type 2 Diabetes: Understanding and Applying the Systematic Review Findings

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AHRQ's Comparative Effectiveness Research on Premixed Insulin Analogues for Adults with Type 2 Diabetes: Understanding and Applying the Systematic Review Findings

Rehan Qayyum, MD, MHS, and Laurence Greene, PhD

Target Audience

Physicians, pharmacists, nurses, and case managers who manage patients with diabetes

Learning Objectives

- Compare the effectiveness, safety, and adherence outcomes of using premixed insulin analogues versus other insulin preparations for achieving optimal glycemic control in type 2 diabetes
- Differentiate the effectiveness and safety of premixed insulin analogues across various subpopulations of patients with type 2 diabetes
- Interpret the effectiveness and safety of premixed insulin analogues in patients receiving oral diabetes medications and with different blood glucose patterns or intensities of control
- Apply AHRQ's systematic review findings on premixed insulin analogues to making patient-centered treatment and management decisions

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DISCLOSURES

Qayyum produced this program under contract with PRIME Education, Inc. (PRIME®). Greene is an employee of PRIME®. The authors report no financial or other conflicts of interest related to the subjects in this report. Mooradian, Jarvis, Gunning, and Valdez report no financial or other conflicts of interest related to the subjects in this report.

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This learning activity was prepared under a dissemination grant from the Agency for Healthcare Research and Quality (AHRQ). The activity is intended to inform clinicians about AHRQ's comparative effectiveness research findings and to identify methods for incorporating the findings into practice. The content in this article is based on the evidence that was available at the time the AHRQ comparative effectiveness report on premixed insulin analogues was prepared (September 2008). The full report is available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/18/106/2008_0915InsulinAnaloguesFinal.pdf.

AHRQ's Comparative Effectiveness Research on Premixed Insulin Analogues for Adults with Type 2 Diabetes: Understanding and Applying the Systematic Review Findings

Rehan Qayyum, MD, MHS, and Laurence Greene, PhD

ABSTRACT

BACKGROUND: Among people with type 2 diabetes who have severe pancreatic β-cell dysfunction, exogenous insulin treatment is essential for controlling glycemia and reducing risks of disease-related complications and mortality. Conventional human insulin preparations are limited by their slow absorption and inability to adequately match the complex basal-bolus pattern of physiologic insulin activity. The development of insulin analogues, including premixed formulations that are designed to mimic physiologic insulin activity, has advanced diabetes management and afforded patients more convenient treatment options. Until recently, however, the benefits and harms of premixed insulin analogues had not been compared with outcomes of other insulin therapies and noninsulin oral antidiabetic agents. In 2008, under the auspices of the Agency for Healthcare Research and Quality (AHRQ), a systematic comparative effectiveness review on this topic was published.

OBJECTIVE: To familiarize health care professionals with the AHRQ comparative effectiveness report on premixed insulin analogues, and to offer and encourage reflections on practical applications of the systematic review findings.

SUMMARY: The comparative effectiveness and safety of premixed insulin analogues vary by comparator therapies and outcomes of interest. The AHRQ systematic review indicated that premixed insulin analogues are more effective than long-acting insulin analogues in lowering postprandial glucose and hemoglobin A1c; however, in this comparison the premixed analogues were associated with higher rates of hypoglycemia and more weight gain. Similar effectiveness and safety findings were obtained through the comparison of premixed insulin analogues and noninsulin antidiabetic drugs. Many comparisons did not yield firm conclusions due to a lack of studies or weak evidence.

According to the most recent National Health and Nutrition Examination Survey (NHANES), approximately 23.6 million people in the United States (nearly 8% of the total population) had diabetes mellitus in 2007.[1] The NHANES ranked diabetes as the seventh leading cause of death among Americans. In the coming decades, the burden of diabetes is expected to rise sharply due to projected increases in high-risk populations, such as the elderly and minority groups. As reported in a dynamic modeling study published in 2010, if trends of recent increases in disease incidence continue, the projected prevalence of diabetes in the United States will be as high as 33% by 2050.[2]

Given its chronic nature, its many complications and comorbidities, and its requirements for continuous medical care and management, diabetes is especially costly. The 2007 NHANES report indicated that the total annual costs associated with diagnosed diabetes in the United States were $174 billion.[1] In an analysis of the medical records of nearly 200,000 members of a large health plan, Menzin et al. (2010) found that although there was not a linear relationship between hemoglobin A1c (A1c) and diabetes-related hospitalization, patients whose A1c exceeded 10% were more likely to have a diabetes-related hospitalization compared with patients whose A1c values were less than 7% (odds ratio [OR] = 2.13, 95% confidence interval [CI] = 1.36–3.33).[3] For these 2 A1c levels, respectively, estimated per-patient costs of a diabetes-related hospitalization were $6,759 and $2,792.

Approximately 90% to 95% of diabetes cases are characterized by type 2 etiopathogenesis, in which hyperglycemia occurs due to a combination of insulin resistance and inadequate compensatory secretion of insulin from pancreatic β cells. Through various mechanisms, chronically elevated blood glucose can damage vascular and neural tissue, causing long-term complications and comorbidities that include retinopathy, with risks of vision loss and blindness; nephropathy and associated renal failure; peripheral neuropathy, with risks of foot ulcers and amputation; and autonomic neuropathy, which can lead to genitourinary and gastrointestinal symptoms as well as sexual dysfunction. Moreover, diabetes-related hyperglycemia is associated with increased risks of cardiovascular and cerebrovascular disease.[4]

Many people with type 2 diabetes can achieve adequate glycemic control through lifestyle interventions and oral antidiabetic medications. However, for patients with severe β-cell dysfunction, exogenous insulin treatment is essential for controlling glycemia and reducing risks of diabetes-related complications and mortality. As reported in the 2005 National Health Interview Survey, 28% of people with type 2 diabetes used exogenous insulin, either alone (16%) or combined with oral antidiabetic agents (12%).[5] Results from the UK Prospective Diabetes Study suggest that within a decade after diabetes diagnosis, the majority of patients will need insulin therapy to achieve A1c levels below 7%.[6]

Numerous exogenous insulin preparations have been developed with the goal of matching, as closely as possible, physiologic patterns of endogenous insulin release. In healthy individuals, insulin is secreted in 2 complementary patterns: (a) a continuous, low-amplitude basal release that maintains blood glucose concentrations between meals and regulates hepatic gluconeogenesis and lipolysis; and (b) rapid, high-amplitude, bolus secretions in response to dietary macronutrient absorption, which protect against severe postprandial blood glucose excursions. Accordingly, insulin preparations are distinguished by their pharmacokinetic properties, including their times

TABLE 1 Pharmacokinetic Characteristics of Selected Insulin Therapies

Insulin Product	Time to Peak Activity (Hours)	Percentage of Total Activity in First 4 Hours	Duration of Action (Hours)
Rapid-Acting Insulin Analogues[a]			
Insulin aspart	1–3	65	3–5
Insulin lispro	0.5–1.5	70	3–4
Intermediate-Acting Human Insulin			
NPH	6–12	14	18–24
Long-Acting Insulin Analogues			
Insulin glargine	No pronounced peak	NA	24
Insulin detemir	6–8	NA	5.7–23.2[b]
Premixed Human Insulin			
NPH/regular insulin 70/30	4.2	25	18–24
NPH/regular insulin 50/50[c]	4.0	54	18–24
Premixed Insulin Analogues			
Insulin aspart 70/30	1–4	45	18–24
Insulin lispro 75/25	2.6	35	18–24
Insulin lispro 50/50	2.3	45	18–24

Adapted from Qayyum et al. (2008).[10]

[a]*Includes insulin glulisine.*

[b]*Shorter and longer duration of action associated with smaller and larger doses, respectively.*

[c]*NPH/regular insulin 50/50 was withdrawn from the U.S. market by the manufacturer in November 2009.*

NPH = neutral protamine Hagedorn.

to onset and peak activity as well as their duration of action (Table 1).

Insulin replacement therapies are limited in their capacity to match physiologic conditions due to the complexity of normal insulin secretion patterns and various pharmacokinetic factors. For example, soluble human insulin preparations aggregate upon injection and are thus absorbed too slowly to protect adequately against postprandial glucose excursions.[7] Intermediate-acting preparations, or neutral protamine Hagedorn (NPH) insulin, are associated with unpredictable peaks. In addition, conventional insulin treatment regimens can pose considerable barriers to adherence. Patients who use both prandial (bolus) and long-acting (basal) insulin may be inconvenienced by demands of multiple daily injections and by having to plan meals and activities based on strict treatment schedules. Some people with diabetes are reluctant to begin and maintain insulin treatment because they anticipate the common side effects hypoglycemia and weight gain.[8]

The relatively recent development of insulin analogues, synthetic insulins produced with recombinant DNA technology, has addressed some of the pharmacokinetic limitations of exogenous human insulin.[9] Diabetes management has also been advanced by novel premixed insulin formulations, which combine a rapid-acting insulin with its slower-acting protaminated form in fixed proportions. Premixed human insulin and premixed insulin analogues are designed to control both fasting and postprandial glucose levels with only 1 injection. While premixed human insulin preparations need to be given 30 minutes before meals, premixed analogues afford greater flexibility because they can be administered either shortly before or immediately after meals. Thus, these formulations may offer advantages to patients who are unwilling to self-administer multiple daily injections or who are at risk of nonadherence due to demands on coordinating treatments with meals.[7,9]

Three premixed insulin analogues are approved for use in the United States: insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50. For each preparation, the first number represents the constituent percentage of protaminated analogue, which acts over 8–12 hours to control basal glucose levels. The second number represents the constituent percentage of soluble rapid-acting analogue for protecting against excessive mealtime glucose excursions.

Whereas the proposed advantages of premixed insulin analogues are indeed sensible, no comprehensive evidence-based analysis of their effectiveness and safety had been conducted until recent years. In 2008, under the auspices of the Agency for Healthcare Research and Quality (AHRQ), a systematic review of existing research was published on the benefits and harms of FDA-approved premixed insulin analogues compared with other insulin preparations and noninsulin antidiabetic drugs for treating type 2 diabetes in adults.[10] The full comparative effectiveness report, along with supplementary publications including a clinician guide and a consumer (patient) guide, is available for download on AHRQ's Effective Health Care Program website at http://effectivehealthcare.ahrq.gov/.

The systematic review of studies on premixed insulin analogues was conducted by the AHRQ-supported Evidence-based Practice Center (EPC) at Johns Hopkins University. The project director, a coauthor of this article, was Dr. Rehan Qayyum. Here we summarize the comparative effectiveness review and offer implications and practical applications of its findings for health care clinicians caring for patients with diabetes, including interprofessional teams in all practice settings.

Key Questions Motivating the Comparative Effectiveness Review

Consistent with AHRQ's procedures for developing all of its comparative effectiveness reports, the topic of premixed insulin analogues was nominated through an open process in which a draft of Key Questions, developed by the AHRQ Scientific Resource Center, was posted on a public website soliciting comments and questions. After reviewing the public feedback, the Scientific Resource Center approved a final set of 4 Key Questions, which are summarized as follows.

- Key Question 1: For optimizing glycemic control in adults

with type 2 diabetes, how effective are premixed insulin analogues compared with the following treatments?
   a. Long-acting insulin analogue monotherapy (insulin detemir or glargine)
   b. Rapid-acting insulin analogue monotherapy (insulin aspart or lispro)
   c. Combined regimens of long-acting and rapid-acting insulin analogues
   d. Premixed human insulin preparations (NPH/regular 70/30 or NPH/regular 50/50)
   e. Intermediate-acting human insulin (NPH) monotherapy
   f. Combined regimens of rapid-acting insulin analogues and intermediate-acting human insulin
   g. Noninsulin antidiabetic agents (e.g., thiazolidinediones, metformin, sulfonylureas, meglinitides, or exenatide)

This first Key Question also entailed comparisons among the 3 premixed insulin analogue formulations.

- Key Question 2: For adults with type 2 diabetes, how do premixed insulin analogues compare with other commonly used insulin and noninsulin antidiabetic therapies with regard to adverse events (hypoglycemia and weight gain) and adherence?
- Key Question 3: Does the effectiveness or safety of premixed insulin analogues vary across the following patient subpopulations?
   a. Elderly (≥65 years) and very elderly (≥85 years) patients
   b. Patients in other demographic groups (e.g., age, gender, and racial groups)
   c. Patients with comorbid medical conditions
   d. Patients with limited life expectancy
   e. Patients with disabilities
- Key Question 4: How effective and safe are premixed insulin analogue regimens for (a) individuals who also take oral noninsulin antidiabetic agents and (b) individuals with varying blood glucose patterns (e.g., fasting hyperglycemia versus postprandial hyperglycemia) or types of glycemic control (e.g., tight control, usual control, or postprandial control)?

Systematic Review Methods

The Johns Hopkins University EPC team followed AHRQ's guidelines for conducting comparative effectiveness reviews of published studies.[11] (AHRQ also supports original research that generates new evidence on the comparative benefits and harms of health care tests, treatments, procedures, and services. The original research is conducted through 2 programs: The DEcIDE—Developing Evidence to Inform Decisions about Effectiveness—research network and the Centers for Education and Research on Therapeutics, or CERTs).

In their strategic approach to searching for published studies on insulin therapies for diabetes, Qayyum et al. used comprehensive databases of biomedical literature, including MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature. The searches covered periods from database inception through February 2008. Published articles and other relevant materials were also obtained through direct searches of relevant medical journals, FDA label information, and public registries of clinical trials. The EPC team limited their search to English-language articles reporting clinical trials and observational studies that compared an FDA-approved premixed insulin analogue with any other drug for adults with diabetes.

Qayyum et al. initially identified 2,202 unique article citations, from which 135 were deemed appropriate for evaluation according to inclusion criteria. Reported studies were excluded if they did not (a) address 1 of the 4 Key Questions, (b) compare a premixed insulin analogue to a commonly used alternative diabetes treatment, and (c) investigate relevant outcomes of diabetes such as common measures of glycemic control, microvascular and macrovascular complications, mortality, adverse effects, adherence, and quality of life. No restrictions were set on study duration or sample size. Through their selection process, which entailed evaluations by 2 independent reviewers, Qayyum et al. identified 45 studies, reported in 50 articles, for inclusion. With the exception of 2 observational studies, all were randomized clinical trials (23 parallel-arm trials and 20 crossover trials). The trials enrolled a total of 14,603 adult patients (ages 51-68 years; median 52% male; initial median A1c value 8.7%).

The EPC team used standardized forms to extract relevant data from the selected studies. Two independent reviewers assessed the quality of each study by applying adapted versions of the Jadad criteria[12] and the Newcastle-Ottawa Scale[13] as well as AHRQ's *Guide for Conducting Comparative Effectiveness Reviews*.[11] Study quality criteria included the extent to which subjects and investigators were blinded about treatments; the validity of data collection methods; the sufficiency of patient follow-up for assessing outcomes of interest; and whether funding sources and conflicts of interest were identified.

In addition to evaluating the quality of study methods, Qayyum et al. graded the quantity, quality, and consistency of the evidence derived from their review. This assessment was based on the guidelines of the GRADE Working Group.[14] For each treatment comparison and outcome, the EPC team graded the strength of evidence at 1 of 3 levels:

- *High*, indicating the reviewers' confidence that further research would be very unlikely to change their confidence in the estimated effect observed in the literature
- *Moderate*, indicating that further research would be likely to have an important impact on the reviewers' confidence in the estimated effect and might even change the

estimates
- *Low*, indicating that further research would be very likely to have an important impact on the reviewers' confidence in the estimated effect and would likely change the estimate

The EPC researchers recognized that the ultimate goal of type 2 diabetes treatment is to help patients achieve the most important clinical outcomes, which entails reducing risks of macrovascular complications (e.g., coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (e.g., diabetic nephropathy, neuropathy, and retinopathy). However, in their systematic review of the literature, Qayyum et al. found no studies that were specifically designed to determine the comparative effects of premixed insulin analogues on these outcomes. Thus, the authors developed a conceptual model for conducting their review that distinguished between (a) *clinical outcomes*, including macrovascular and microvascular complications, and all-cause mortality, cardiovascular mortality, and cardiovascular morbidity; and (b) *intermediate outcomes*, including fasting blood glucose concentration, postprandial blood glucose concentration, and A1c percentages. (Evidence-based associations between intermediate and clinical outcomes are addressed later in this article.)

In the main approach to their data extraction, the EPC researchers recorded treatment-group changes in key outcomes from each study's baseline to endpoint; differences in these changes between treatment groups were then used in statistical analyses. When 2 or more trials making a specific comparison were identified, Qayyum et al. conducted meta-analyses of the data, which elicited weighted mean differences in outcomes between patients treated with premixed insulin analogues versus comparator therapies. For reasons that the authors detail in their full report,[10] the pooled analyses were based on a random-effects model.

Before the final comparative effectiveness review was published in 2008, a draft underwent independent peer review. In addition, the draft was posted on a public Web site; appropriate public comments and suggestions were incorporated into the final publication.

Comparative Effectiveness and Safety of Premixed Insulin Analogues

In this section we summarize Qayyum and coworkers' systematic review findings that address Key Questions 1 and 2. In our presentations of pooled mean differences in glycemic measures between treatment groups, values preceded by minus signs reflect more beneficial outcomes for patients treated with premixed insulin analogues, and positive values reflect more beneficial outcomes for patients treated with designated comparators. Key overall findings are presented in Table 2.

Intermediate Outcomes: Fasting Blood Glucose, Postprandial Blood Glucose, and A1c

Appropriate clinical applications of research on diabetes therapies depend on understanding the relevance of standard measures of dysglycemia. As updated in the 2010 American Diabetes Association report on the diagnosis and classification of diabetes mellitus, the following criteria provide evidence-based diagnostic guidelines: (a) A1c ≥6.5%; or (b) fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), where fasting is defined as refraining from caloric intake for at least 8 hours; or (c) postprandial plasma glucose (2 hours) ≥200 mg/dL (11.1 mmol/L) assessed with an

TABLE 2

Comparative Effectiveness of Premixed Insulin Analogues: Glycemic Control Measures and Adverse Effects

	Comparing		Comparing		Comparing	
	PMIA	Long-Acting Analogues	PMIA	Premixed Human Insulin	PMIA	Noninsulin Drugs
Better at Lowering Fasting Glucose		●●	No difference ●●		●●	
Better at Lowering Postprandial Glucose	●●●		●●●		●●	
Better at Lowering A1c	●●●		No difference ●●●		●●	
Lower Rates of Hypoglycemia		●●●	No difference ●●●			●●●
Less Weight Gain		●●	No difference ●●			●●

Source: Qayyum et al. (2008).[10]

●●=Moderate strength of evidence; ●●●=High strength of evidence.

PMIA=premixed insulin analogue.

oral glucose tolerance test; or, for patients with classic symptoms of hyperglycemia or hyperglycemic crisis, (4) random plasma glucose ≥200 mg/dL (11.1 mmol/L).[15]

Published in 2010, a comprehensive meta-analysis of 102 multinational studies identified associations between fasting blood glucose concentration and risks of coronary heart disease (CHD), stroke, and death due to vascular diseases.[4] The studies followed a total of nearly 700,000 people who were grouped by whether they had or lacked a history of diabetes at baseline. Diabetes was associated with approximate 2-fold increases in the risks of CHD and ischemic stroke. Among study participants who originally did not have diabetes, over a median period of 10.8 years to first vascular disease outcomes, there was no association between vascular risk and baseline fasting glucose concentrations from 3.90–5.59 mmol/L (70.20–100.62 mg/dL). Relative to this designated reference range, risks of CHD increased by (a) 11% for 5.60–6.09 mmol/L (100.80–109.62 mg/dL; hazard ratio [HR] = 1.11; CI = 1.04–1.18); (b) 17% for 6.10–6.99 mmol/L (109.80–125.82 mg/dL; HR = 1.17; CI = 1.08–1.26); and (c) 78% for concentrations above 6.99 mmol/L (125.82 mg/dL; HR = 1.78; CI = 1.56–2.03). As interpreted by the study authors, these findings indicate a modest nonlinear relationship between fasting blood glucose and cardiovascular disease risk.

A1c, which reflects glycemic control over a period of 2 to 3 months prior to its measurement, is commonly recognized as the best marker of dysglycemia and microvascular complications in diabetes.[16] A strong association between baseline A1c and risks of CHD and stroke was identified through the Atherosclerosis Risk in Communities (ARIC) study, a long-term prospective cohort analysis of nearly 16,000 people.[17] Over a median follow-up period of approximately 14 years, the incidence of newly diagnosed diabetes ranged from 6% to 79% in participants whose baseline A1c values were lower than 5% and higher than 6.5%, respectively. Risks of developing CHD were determined in relation to a reference group of study participants whose baseline A1c values ranged from 5.0% to 5.5%. Among a subset of study participants (n = 11,092) with baseline A1c values less than 5.0% and greater than 6.5%, respectively, adjusted HRs for CHD were 0.96 (CI = 0.74–1.24) and 1.95 (CI = 1.53–2.48). The ARIC study also indicated that cardiovascular disease risk and all-cause mortality were more strongly associated with A1c percentage than with fasting blood glucose concentration.

In a seminal study on the contributions of fasting and postprandial glucose excursions to dysglycemia in type 2 diabetes, 290 patients were grouped into 1 of 5 equal quintiles based on their A1c values.[18] Quintiles ranged from <7.3% to >10.2%. The contribution of diurnal postprandial glucose levels to overall hyperglycemia decreased significantly from the first to the fifth A1c quintile. In contrast, the contribution of fasting glucose levels to overall hyperglycemia increased significantly across the 5 quintiles. These results suggest that for patients with relatively moderate hyperglycemia and lower A1c values, it is especially important for therapeutic strategies to target the control of postprandial glucose excursions.[9]

The majority of studies included in the AHRQ systematic review reported outcomes of fasting glucose, postprandial glucose, and A1c. For fasting glucose, studies reported either concentrations without indicating time of day, pre-breakfast concentrations, or pre-breakfast and pre-dinner concentrations. In their primary analysis of fasting glucose outcomes, Qayyum et al. combined unspecified timing and pre-breakfast blood glucose levels; pre-dinner levels were analyzed separately. For postprandial glucose, the EPC researchers grouped studies that reported levels between 90–120 minutes after a meal.

Premixed Insulin Analogues Versus Long-Acting Insulin Analogues

For this comparison, Qayyum et al. identified numerous studies that investigated changes in fasting blood glucose, postprandial glucose, and/or A1c:

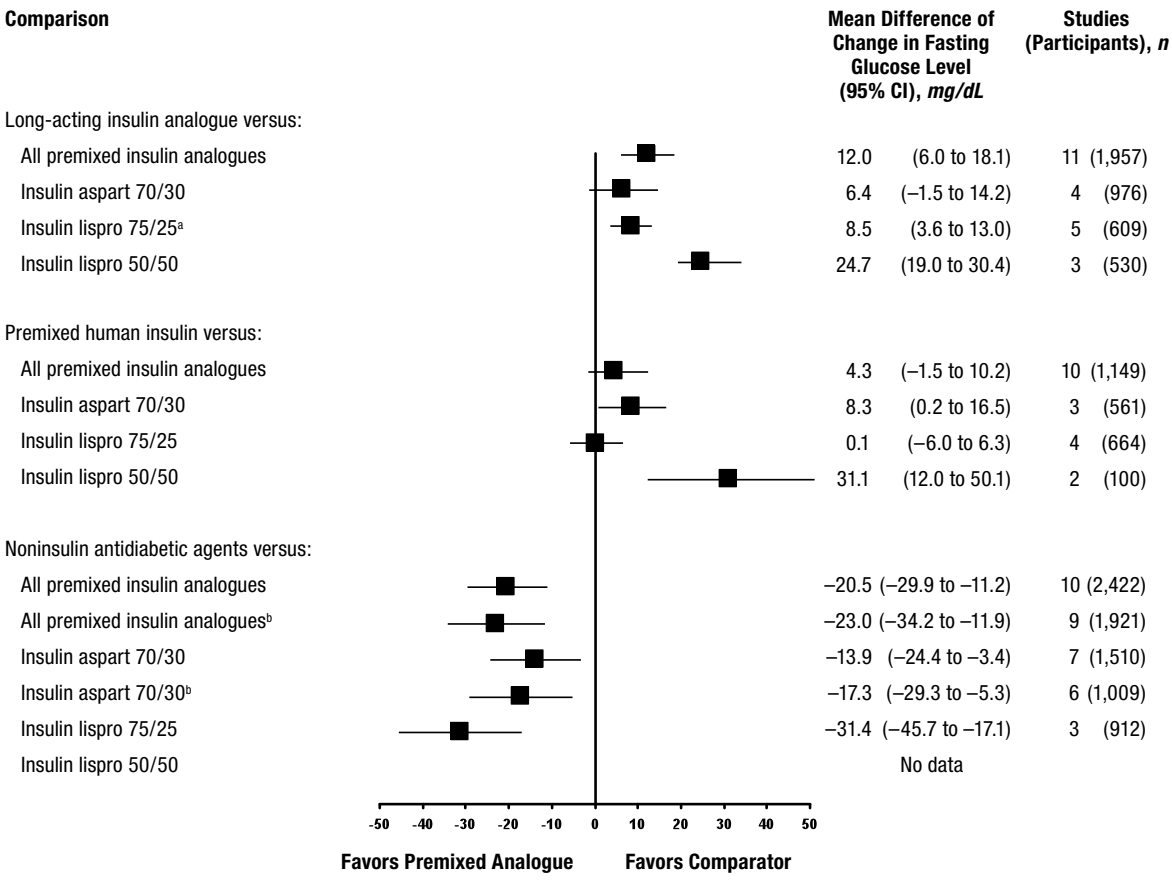
- Insulin aspart 70/30—4 randomized parallel-arm studies that compared insulin aspart 70/30 with insulin detemir[19] or insulin glargine[20-22]
- Insulin lispro 75/25—5 randomized crossover trials[23-27] and 1 observational study that compared insulin lispro 75/25 to insulin glargine[28]
- Insulin lispro 50/50—3 randomized trials that compared insulin lispro 50/50 to insulin glargine[24,29,30]

In some of the studies, patients in both treatment arms also used noninsulin antidiabetic agents. The duration of follow-up in the clinical trials ranged from 24 weeks to 1 year. At the conclusion of several studies, the insulin dose differed significantly between the premixed analogue arm and the long-acting analogue arm; typically, doses were greater among patients treated with premixed insulin analogues. This methodological issue is attributed to designs that permitted investigators to adjust doses to optimize glycemic control in individual patients.

Based on their pooled analysis of the 11 studies that met selection criteria, Qayyum et al. concluded that premixed insulin analogues may be less effective than long-acting insulin analogues in lowering fasting blood glucose concentrations (Figure 1). In 3 trials that compared insulin aspart 70/30 with insulin glargine, no significant differences were observed between groups for changes in fasting glucose from baseline to study completion.[20-22] In contrast, the results from a study conducted by Holman et al. (2007) indicated that premixed insulin aspart 70/30 was less effective than long-acting insulin detemir.[19] In patients receiving the 2 treatments, respectively, mean changes in blood glucose were −45 mg/dL and −59 mg/dL (P<0.001).

For the 5 randomized controlled trials that compared insulin lispro 75/25 with long-acting insulin glargine, the

FIGURE 1 Weighted Mean Differences in Fasting Blood Glucose Changes from Studies Comparing Premixed Insulin Analogues with Other Antidiabetes Therapies



Error bars represent 95% CIs. To convert glucose values to mmol/L, multiply by 0.0555.

[a]*Pooled results include those of a study[24] that administered insulin lispro 50/50 in the morning and afternoon and insulin lispro 75/25 in the evening.*

[b]*Reference 55 was excluded.*

Source: Qayyum R, et al. Ann Intern Med. 2008;149(8):549-59.[63] Used by permission.

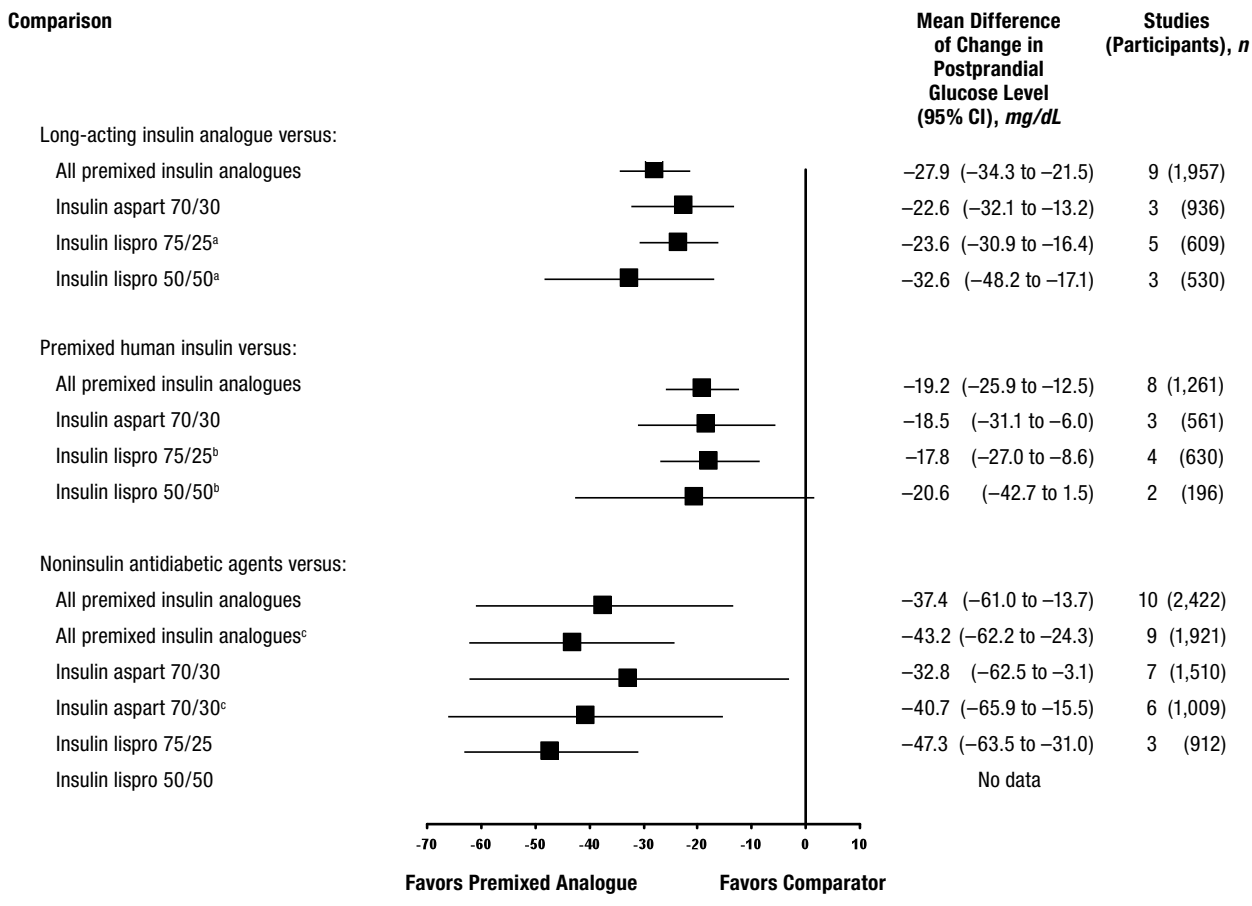
pooled analysis of fasting glucose changes favored insulin glargine (8.5 mg/dL; 95% CI=3.6 to 13.3 mg/dL; *P*=0.001).[23-27] Similar results were obtained from 2 trials that compared insulin lispro 50/50 and insulin glargine; the long-acting analogue alone was more effective than the premixed analogue for lowering fasting glucose.[29,30] In these 2 trials, reductions in fasting glucose concentrations were 30.6 mg/dL[29] and 28.9 mg/dL[30] greater in patients who received insulin glargine than in patients who received insulin lispro 50/50 (*P*<0.001 for comparisons in both studies).

Based on one of the most consistent findings in their review, Qayyum et al. concluded that premixed insulin analogues are more effective than long-acting insulin analogues alone in lowering postprandial glucose (Figure 2). The strength of evidence supporting this conclusion was determined to be high. In pooled analyses, the mean group differences in reductions of postprandial glucose consistently favored the premixed formulations:

- Insulin aspart 70/30 (–22.6 mg/dL; 95% CI=–32.1 to –13.2 mg/dL; *P*<0.001)
- Insulin lispro 75/25 (–23.6 mg/dL; 95% CI=–30.9 to –16.4 mg/dL; *P*<0.001)
- Insulin lispro 50/50 (–32.6 mg/dL; 95% CI=–48.2 to –17.1 mg/dL; *P*<0.001)

Similar to the findings for postprandial glucose concentrations, premixed insulin analogues were consistently more effective than long-acting insulin analogues in lowering A1c (Figure 3). The strength of evidence for this outcome was

FIGURE 2 Weighted Mean Differences in Postprandial Blood Glucose Changes from Studies Comparing Premixed Insulin Analogues with Other Antidiabetes Therapies



Error bars represent 95% CIs. To convert glucose values to mmol/L, multiply by 0.0555.

[a]*Pooled results include those of a study that administered insulin lispro 50/50 in the morning and afternoon and insulin lispro 75/25 in the evening.*[24]

[b]*Pooled results include those of a study that administered insulin lispro 50/50 in the morning and insulin lispro 75/25 in the evening.*[38]

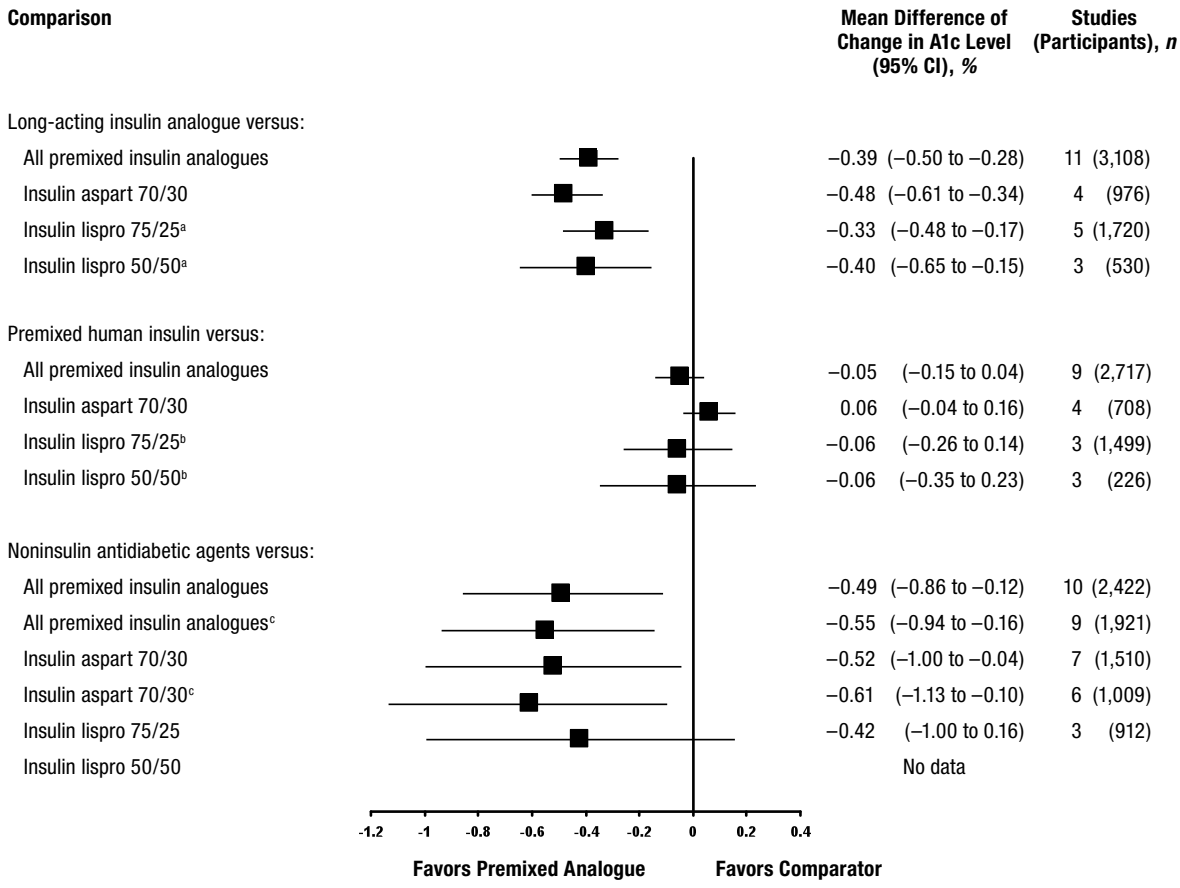
[c]*Reference 55 was excluded.*

Source: Qayyum R, et al. Ann Intern Med. 2008;149(8):549-59.[63] *Used by permission.*

determined to be high. In 3 of 4 trials comparing insulin aspart 70/30 to insulin detemir or glargine, the premixed analogue was associated with significantly greater A1c reductions. The trial that did not reveal a significant between-group difference was limited by a small number of subjects (n=23).[21] In 1 of the 3 trials indicating significant differences, patients treated with insulin aspart 70/30 were more likely to attain target A1c measures of 6.5% or lower than patients treated with insulin detemir (P=0.001).[19] A pooled analysis of the 4 studies on insulin aspart 70/30 yielded a mean treatment-group difference of −0.48% (95% CI=−0.61 to −0.34%; P<0.001).

In 4 clinical trials[23-26] and 1 retrospective observational study[28] that compared insulin lispro 75/25 to insulin glargine, the premixed analogue was associated with significantly greater reductions in A1c (pooled mean difference=−0.33%; 95% CI=−0.48 to −0.17%; P<0.01). The mean differences observed in the clinical trials (range=−0.26% to −0.60%) were relatively greater than the difference observed in the observational study (−0.10%). One of the clinical trials revealed that more patients treated with insulin lispro 75/25 than with insulin glargine reached A1c values of ≤7% (42% versus 18% of patients, respectively; P<0.001).[25] In 3 trials comparing premixed insulin lispro 50/50 to long-acting insulin glargine, reductions in A1c were greater among patients receiving the premixed analogue (pooled mean difference=−0.4%; 95% CI=−0.65% to −0.15%; P=0.002).[24,29,30]

FIGURE 3 *Weighted Mean Differences in A1c Changes from Studies Comparing Premixed Insulin Analogues with Other Antidiabetes Therapies*



Error bars represent 95% CIs.

[a]*Pooled results include those of a study[24] that administered insulin lispro 50/50 in the morning and afternoon and insulin lispro 75/25 in the evening.*

[b]*Pooled results include those of a study[38] that administered insulin lispro 50/50 in the morning and insulin lispro 75/25 in the evening.*

[c]*Reference 55 was excluded.*

Source: Qayyum R, et al. Ann Intern Med. 2008;149(8):549-59.[63] Used by permission.

Premixed Insulin Analogues Versus Rapid-Acting Insulin Analogues

For this comparison, Qayyum and coworkers' literature search identified only 2 studies, 1 on insulin aspart 70/30[19] and 1 on insulin lispro 50/50.[29] In a randomized controlled trial, Holman et al. (2007) investigated changes in fasting blood glucose concentrations in 235 patients treated with insulin aspart 70/30 and 239 patients treated with rapid-acting insulin aspart; patients in both groups also used metformin and a sulfonylurea with meals.[19] The 1-year followup results indicated that the premixed analogue was more effective than its rapid-acting component alone in reducing fasting glucose (mean difference=−22.0 mg/dL; $P<0.001$). In the single trial comparing insulin lispro 50/50 to rapid-acting insulin lispro, no difference in fasting glucose was observed.[29] Based on these findings, Qayyum et al. concluded that premixed analogues may be at least as effective as rapid-acting analogues for lowering fasting glucose.

In contrast to their results for fasting glucose, Holman et al. (2007) found that reductions in postprandial blood glucose were greater for rapid-acting insulin aspart than for insulin aspart 70/30 (mean difference=15 mg/dL; $P<0.001$).[19] However, in a study conducted by Kazda et al. (2006), no difference was observed in postprandial glucose change among patients treated with insulin lispro 50/50 and rapid-acting insulin lispro.[29] Due to the weak evidence in published studies, the EPC researchers could not reach a conclusion

Clinical Reflection: Statistical Versus Clinical Significance

Regarding potential applications of comparative effectiveness research, an essential question involves the clinical significance of the findings, or the extent to which they might translate into meaningful health outcomes in patient populations of interest. Consider, for example, Qayyum and coworkers' finding that, in a pooled analysis of 5 randomized clinical trials, insulin lispro 75/25 was less effective than long-acting insulin analogues in lowering fasting blood glucose. This measure was reduced, on average, by 8.5 mg/dL more in patients treated with long-acting insulin glargine than with the premixed analogue. Whereas this outcome was statistically significant ($P=0.001$), an assessment of its clinical significance depends on its correlation with relevant clinical endpoints, such as reductions in cardiovascular disease risk.

The AHRQ review on premixed insulin analogues was not designed to determine correlations between changes in glycemic measures and clinical endpoints. However, as summarized earlier in this article, a collaborative meta-analysis of 102 prospective studies involving nearly 700,000 people revealed a modest nonlinear association between increases in fasting glucose and cardiovascular disease risk.[4] Based on the assumption of a log-linear relationship above the threshold of 101 mg/dL (an assumption that the authors acknowledged could not be confirmed or refuted by the available data), the meta-analysis authors estimated that every 18 mg/dL reduction in fasting glucose corresponded to a 10.7% decrease in CHD risk (hazard ratio for each increase of 18 mg/dL = 1.12). Generalizing this relationship to the study populations included in the AHRQ review, a mean 8.5 mg/dL advantage for lowering blood glucose (as observed for long-acting glargine in its comparison with lispro 75/25) would be associated with a 5.05% reduction in CHD risk. The validity of this generalization would need to be determined through future studies that are specifically designed to evaluate relationships between changes in glycemic measures and cardiovascular risk in patients treated with premixed insulin analogues.

about the effectiveness of premixed analogues versus rapid-acting analogues in lowering postprandial glucose. For the same reason, conclusions were also not drawn in assessing the effects of premixed analogues versus rapid-acting analogues on A1c.

Premixed Insulin Analogues Versus Combined Regimens of Long-Acting and Rapid-Acting Insulin Analogues

Qayyum et al. identified 2 trials investigating changes in fasting glucose, postprandial glucose, and A1c in patients treated with a premixed analogue versus the combination of a long-acting (basal) and rapid-acting (bolus) analogue.[31,32] The findings of these 2 studies were inconsistent. Moreover, for all 3 intermediate outcomes, the strength of evidence was low; thus, the review authors were unable to reach any firm conclusions regarding this comparison.

Premixed Insulin Analogues Versus Premixed Human Insulin

For this comparison, numerous studies were identified with results indicating changes in fasting blood glucose, postprandial blood glucose, and/or A1c:

- Insulin aspart 70/30 versus NPH/regular 70/30–3 parallel-arm trials[31,33,34] and 3 crossover trials[35-37]
- Insulin lispro 75/25 versus NPH/regular 70/30 or NPH/regular 50/50–9 randomized crossover studies[37-45] and 1 retrospective observational study[28]
- Insulin lispro 50/50 versus NPH/regular 70/30 or NPH/regular 50/50–3 randomized crossover studies[38,41,46] and 1 parallel-arm study[47]

The studies varied considerably in therapy administration methods, dosing schedules, and duration.

For fasting blood glucose concentration, the results differed across the 3 premixed insulin analogue preparations. Insulin aspart 70/30 was less effective than premixed human insulin in reducing fasting glucose (pooled mean difference=8.3 mg/dL; 95% CI=0.16 to 16.5 mg/dL; $P=0.04$). In 1 of 2 trials on insulin lispro 50/50,[47] no difference in fasting glucose change was observed between the premixed analogue and NPH/regular 70/30. However, in the second trial,[46] insulin lispro 50/50 was less effective than the premixed human insulin preparation (mean difference=30.0 mg/dL; $P<0.001$). Finally, no difference in fasting glucose change was found in patients treated with insulin lispro 75/25 versus a premixed human insulin preparation. The pooled analysis of all relevant studies indicated no significant difference between premixed insulin analogues and premixed human insulin in lowering fasting blood glucose (pooled mean difference=4.3 mg/dL; 95% CI=−1.5 to 10.2 mg/dL; $P>0.05$).[63] The strength of evidence for all analyses involving fasting glucose was rated as moderate.

More robust and consistent evidence, rated by Qayyum et al. as strong, was derived from their analyses of postprandial glucose changes. For this outcome, all 3 premixed insulin analogues were more effective than premixed human insulin. As indicated by the following pooled differences, the analogues lowered postprandial glucose to a considerably greater extent than did the human insulin preparations.

- Insulin aspart 70/30 (–18.5 mg/dL; 95% CI=–31.1 to –6.0 mg/dL; $P=0.004$)
- Insulin lispro 75/25 (–17.8 mg/dL; 95% CI=–27.0 to –8.6 mg/dL; $P<0.001$)
- Insulin lispro 50/50, postprandial glucose measured post-breakfast and post-dinner (–30.3 mg/dL; 95% CI=–55.6 to –5.0 mg/dL; $P=0.02$)
- Insulin lispro 50/50, postprandial glucose measured post-dinner only (–20.6 mg/dL; 95% CI=–42.7 to 1.5 mg/dL; $P>0.05$)

Clinical Reflection: Controlling Fasting Versus Postprandial Glucose

Whereas both fasting and postprandial glucose must be controlled to prevent diabetes-related complications and mortality, therapeutic strategies targeting one or the other measure may be appropriate depending on the individual patient's disease status. As summarized earlier, evidence indicates that the contribution of postprandial glucose excursions to overall dysglycemia is greatest in patients who have relatively low A1c values (closer to 7%).[18] In contrast, the contribution of fasting glucose excursions to overall dysglycemia appears to be greatest in patients with high A1c values (closer to 10%). This knowledge may aid clinicians in applying the findings from the AHRQ systematic review that indicate inconsistent effects of selected premixed insulin analogues on fasting versus postprandial glucose. For example, compared with premixed human insulin, insulin aspart 70/30 was less effective in lowering fasting glucose but more effective in lowering postprandial glucose. Given the evidence that postprandial glucose control may be more important when A1c levels are low, a clinician might decide that, for patients who require insulin but whose hyperglycemia is not severe, the premixed insulin analogue would be most appropriate. However, at the same time the clinician should consider that pooled analyses indicated no difference in the effects of insulin aspart 70/30 and premixed human insulin for lowering A1c.

For A1c, the pooled analysis of study results indicated no difference in the effectiveness of premixed insulin analogues versus premixed human insulin.

Premixed Insulin Analogues Versus (a) Combined Regimens of Rapid-Acting Insulin Analogues and Intermediate-Acting Human Insulin and (b) Intermediate-Acting Human Insulin Alone

For these 2 sets of comparisons, either no studies were identified or the available evidence was too weak to support any viable conclusions regarding changes in fasting blood glucose, postprandial glucose, and A1c. The systematic review included 2 studies that compared the effects of insulin aspart 70/30 with intermediate-acting human insulin (NPH) on blood glucose changes.[33,48] The mean group differences in fasting glucose reductions were 2 mg/dL[48] and 16 mg/dL[33] ($P>0.05$ for comparisons in both studies). Similarly, both studies reported no significant differences in postprandial glucose and A1c in patients treated with insulin aspart 70/30 versus NPH insulin.

Premixed Insulin Analogues Versus Noninsulin Antidiabetic Agents

Qayyum et al. identified 10 studies making this comparison and providing data for changes in fasting blood glucose, postprandial blood glucose, and/or A1c:

- Insulin aspart 70/30—a total of 7 studies in which the comparators were a thiazolidinedione plus glibenclamide;[49,50] metformin plus glibenclamide;[51] either monotherapy with, or any combination of, a sulfonylurea, metformin, or meglitinide;[52] metformin, sulfonylurea, or meglitinide alone or a combination of any 2 of these agents;[53] metformin plus pioglitazone;[54] and exenatide[55]
- Insulin lispro 75/25—3 randomized parallel-arm studies in which the comparators were a fixed dose of glibenclamide;[56] glibenclamide plus metformin, the latter of which was also used by patients in the insulin lispro 75/25 group;[57] and a fixed dose of glyburide[58]

No studies were identified that compared insulin lispro 50/50 with a noninsulin diabetic agent.

In analyses of changes in fasting blood glucose concentrations, moderately strong evidence indicated that premixed insulin analogues were more effective than noninsulin antidiabetic agents. The pooled mean differences were as follows:

- Insulin aspart 70/30 (–13.9 mg/dL; 95% CI=–24.4 to –3.4 mg/dL; $P=0.009$)
- Insulin lispro 75/25 (–31.4 mg/dL; 95% CI=–45.7 to –17.1 mg/dL; $P<0.001$)

A notable exception involved the incretin mimetic exenatide, which did not differ from insulin aspart 70/30 in lowering fasting glucose.[55] Because exenatide is an injectable noninsulin antidiabetic agent, Qayyum et al. performed separate pooled analyses comparing premixed insulin analogues versus noninsulin agents with and without exenatide.

Pooled analyses of postprandial (after dinner) blood glucose changes also indicated a greater effectiveness of premixed insulin analogues versus most noninsulin diabetic agents:

- Insulin aspart 70/30 (–32.8 mg/dL; 95% CI=–62.5 to –3.1 mg/dL; $P=0.03$)
- Insulin lispro 75/25 (–47.3 mg/dL; 95% CI=–63.5 to –31.0 mg/dL; $P<0.001$)

As was true for fasting glucose, no differences in postprandial glucose changes were observed between patients treated with insulin aspart 70/30 and exenatide.[55]

For lowering A1c, the pooled analysis including all premixed analogues indicated their better effectiveness compared with all noninsulin antidiabetic agents (mean difference=–0.50%; 95% CI=–0.9% to –0.10%; $P=0.034$).[63] However, exceptions were evident in the individual studies comprising this analysis. For example, no differences were observed for A1c reductions among patients treated with insulin aspart 70/30 versus glibenclamide and pioglitazone[49] or in patients treated with insulin aspart 70/30 plus rosiglitazone versus rosiglitazone plus glibenclamide.[50] In another study,[55] insulin aspart 70/30 was less effective than exenatide in lowering A1c, with the results approaching the predetermined criterion for statistical significance (mean difference=0.15%; $P=0.07$). Inconsistent findings

also characterized the individual studies comparing insulin lispro 75/25 with noninsulin antidiabetic agents.

Comparisons Among Premixed Insulin Analogues

Four studies were identified that compared one premixed insulin analogue to another:

- Insulin aspart 70/30 versus insulin lispro 75/25–2 randomized crossover studies[37,59]
- Insulin lispro 75/25 versus insulin lispro 50/50–1 randomized crossover study[41]
- Insulin lispro 75/25 versus morning insulin lispro 50/50 plus dinner insulin lispro 75/25–1 randomized crossover study[60]

No treatment-group differences were observed for changes in fasting blood glucose. However, 2 studies indicated that postprandial glucose concentration was reduced to a greater extent in patients treated with insulin lispro 50/50 than with insulin lispro 75/25 ($P<0.05$ and $P=0.001$, respectively).[41,60] In the 1 study that evaluated A1c changes, insulin lispro 75/25 lowered values to a greater extent than did insulin aspart 70/30; however, the difference did not meet the predetermined criterion for statistical significance (mean difference=0.14%; $P=0.08$).[59] Given the lack of sufficient evidence in the published literature, Qayyum et al. were unable to reach firm conclusions about the comparative effectiveness of one premixed analogue over another for optimizing glycemic control.

Clinical Reflection: Patient Access to Insulin and Noninsulin Diabetes Therapies

The AHRQ systematic review findings may have preliminary applications to pharmacists in managed care plans. For managing access to insulin therapies, formulary management decisions are sometimes unclear. As the review indicates, most premixed insulin analogues are more effective at lowering glucose levels than most oral antidiabetic drugs; however this comes at a recognized potential increased risk of hypoglycemia or weight gain. Long-acting insulin analogues or nighttime NPH can act as a bridge between oral antidiabetic drugs and premixed insulins. Long-acting insulins, requiring a single subcutaneous injection daily, may be more acceptable to patients than premixed insulin analogues, which can require multiple injections. Long-acting insulins also carry a slightly lower risk of hypoglycemia and weight gain, desirable considerations for patients naïve to insulin regimens. Therefore a health plan should consider the use of insulins when such therapy can bring about the incremental change needed for additional glucose lowering. The analogue insulins are generally more expensive and may come with higher copayments for the patient. This information may also be considered when developing a treatment pathway for the patient in a managed care environment.

–Diana I. Brixner, RPh, PhD

Adverse Effects: Hypoglycemia and Weight Gain

Two of the most commonly reported side effects of insulin therapy are hypoglycemia and weight gain; these were the main adverse outcomes studied in Qayyum and coworkers' systematic review. For both of these outcomes, comparisons between premixed insulin analogues and other therapies were often limited by a lack of evidence. Thus, in many cases, the EPC researchers could not draw conclusions.

Premixed Insulin Analogues Versus Long-Acting Insulin Analogues

Compared with long-acting analogues, premixed analogues were generally associated with significantly greater incidences of hypoglycemia (high strength of evidence) and more weight gain (moderate strength of evidence). In a study comparing insulin aspart 70/30 with insulin detemir, overall hypoglycemia was reported in 91.9% of patients treated with the premixed analogue (n=235) versus 73.9% (n=234) of patients treated with the long-acting analogue ($P<0.001$).[19] In a pooled analysis of 3 studies comparing insulin aspart 70/30 with insulin glargine, rates of minor hypoglycemia were significantly higher in the groups treated with the premixed formulation (OR=2.8; 95% CI=1.4 to 5.4; $P=0.003$).[20-22] No difference was observed between these 2 therapies for the incidence of symptoms-only hypoglycemia.

Three trials comparing insulin lispro 75/25 with insulin glargine revealed mixed findings with regard to rates of treatment-related hypoglycemia. Whereas 1 study reported no difference in episodes of overall hypoglycemia per patient,[26] 2 studies indicated significantly greater rates of this adverse effect in patients treated with insulin lispro 75/25.[24,25] Analyses of minor hypoglycemia risk also revealed mixed findings for insulin lispro 75/25 versus insulin glargine. In 3 trials comparing insulin lispro 50/50 and insulin glargine, consistently higher risks of overall hypoglycemia were observed among patients treated with the premixed analogue.[24,29,30] As a representative example, Robbins et al. (2007) reported cases of overall hypoglycemia in 28.7% and 17.8% of patients treated with insulin lispro 50/50 and insulin glargine, respectively ($P=0.02$).[30]

Four trials investigated the effects of insulin aspart 70/30 versus a long-acting insulin analogue on body weight changes.[19,20-22] A pooled analysis of these studies indicated that patients treated with the premixed analogue gained significantly more weight over periods of 6 months to 1 year (mean difference=2.5 kg; 95% CI=1.6 to 3.4 kg; $P<0.001$). The results from 2 trials comparing insulin lispro 50/50 and insulin glargine were mixed.[29,30] In 1 of these studies,[30] patients treated with the premixed analogue gained significantly more weight than patients treated with the long-acting analogue (mean difference=1.7 kg; $P<0.001$). In the other study, changes in body mass index did not differ significantly across treatment arms (mean difference=0.4 kg/m^2; $P=0.19$).[29]

Take-Home Messages: Premixed Insulin Analogues Versus Long-Acting Insulin Analogues

For lowering postprandial glucose and A1c, premixed analogues are more effective than long-acting analogues alone (●●●).

However, long-acting analogues alone are (a) more effective than premixed analogues at lowering fasting blood glucose (●●) and (b) associated with lower rates of hypoglycemia (●●●) and less weight gain (●●).

●●=Moderate strength of evidence
●●●=High strength of evidence

Premixed Insulin Analogues Versus Rapid-Acting Insulin Analogues

Because few studies made this comparison, Qayyum et al. were unable to reach a firm conclusion for the outcome of hypoglycemia. In the only study that compared insulin aspart 70/30 with rapid-acting insulin aspart, no difference was observed in the incidence of hypoglycemia between the 2 groups.[19] In a study comparing insulin lispro 50/50 with its rapid-acting component, hypoglycemia incidence was greater in the rapid-acting analogue arm (53.8%) than in the premixed analogue (44.4%) arm (the original study authors did not report a *P* value for this analysis).[29]

For minimizing the adverse effect of weight gain, Qayyum et al. concluded that premixed insulin analogues may be more advantageous than rapid-acting analogues. In 1 study, less weight gain was associated with insulin aspart 70/30 than with rapid-acting insulin aspart (mean difference=−1.0 kg; P=0.005).[19] In agreement, the results of another study indicated that BMI increased to a lesser extent in the insulin lispro 50/50 arm than in the rapid-acting insulin lispro arm (mean difference=−0.3 kg/m^2; P=0.048).[29]

Premixed Insulin Analogues Versus Combined Regimens of Long-Acting and Rapid-Acting Insulin Analogues

For this comparison, 2 studies were identified that addressed outcomes of hypoglycemia and weight gain.[32,61] Joshi et al. (2005) reported no major hypoglycemic events.[61] However, compared with the combination of insulin glargine and rapid-acting insulin aspart, insulin aspart 70/30 was associated with a lower incidence of minor hypoglycemic events (58.0% versus 16.7% of patients, respectively; P<0.05). In contrast, Rosenstock et al. (2008) found no differences in the rates of overall, nocturnal, and severe hypoglycemia between patients treated with insulin lispro 50/50 versus a combined long-acting and rapid-acting regimen.[32] Both studies reported no differences in weight gain between patients who received the 2 treatments.

Premixed Insulin Analogues Versus Premixed Human Insulin

For this comparison, individual trials and pooled analyses revealed no significant treatment-group differences in the incidence of hypoglycemia (high strength of evidence) and weight gain (moderate strength of evidence).

Clinical Reflection: Weighing the Benefits and Harms of Premixed Insulin Analogues

Two frequent clinical scenarios reflect the benefits and harms of premixed insulin analogues. First, consider the patient with an A1c value greater than 8% and significant elevations in postprandial blood glucose despite treatment with the maximum dose of oral noninsulin agents, such as a sulfonylurea plus metformin. The patient is hesitant to use insulin because she fears needles and has an extremely busy work schedule, which she perceives as a major barrier to adherence. The addition of once-daily basal insulin may quickly bring the patient's elevated fasting blood glucose to target values, but the issue of treating postprandial glucose excursions lingers. As such, initiating treatment with a premixed insulin analogue will afford a minimum number of daily injections to control both fasting and postprandial blood glucose. While achieving tight control may be difficult, this method may appeal to patients who are seeking a decrease in A1c without multiple daily injections.

A second scenario is also common in the care of patients. Often, patients having reached the above scenario with A1c and maximum oral treatments are placed on basal insulin, titrated to a fasting blood glucose target. Patients may achieve this goal relatively easily with careful titration. It is disappointing to patient and provider alike, then, when the A1c value is still elevated, reflecting poor postprandial blood glucose control in the face of well-controlled fasting blood glucose values. The decision point at this time is either to add multiple daily (up to 3) rapid-acting insulin analogue injections in addition to the basal insulin, or switch to 2 shots daily of a premixed insulin analogue. While the decision should be based on the patient's goals, values and beliefs about therapy, for many patients, a complicated regimen of multiple shots daily, carbohydrate counting, and meal planning is not compatible with their personal goals. While the cost may be a loss of flexibility in matching insulin to meals, there is more flexibility with this regimen of premixed insulin analogues than with premixed human insulin, due to a more rapid onset and shorter duration.

As with the addition of any insulin-based regimen, adverse effects such as weight gain and hypoglycemia are the consequence of more frequently approaching ideal blood glucose concentrations compared with lingering at higher blood glucose values that may contribute to long-term morbidity and mortality costs.

–Karen M. Gunning, PharmD

Take-Home Messages: Premixed Insulin Analogues Versus Premixed Human Insulin

For lowering postprandial glucose, premixed analogues are more effective than premixed human insulin (●●●).

For other measures of glycemic control and for adverse effects, no differences were identified between premixed analogues and premixed human insulin.

●●=Moderate strength of evidence

●●●=High strength of evidence

Premixed Insulin Analogues Versus (a) Combined Regimens of Rapid-Acting Insulin Analogues and Intermediate-Acting Human Insulin and (b) Intermediate-Acting Human Insulin

For these 2 sets of comparisons, a lack of studies or weak evidence precluded firm conclusions regarding the adverse outcome of hypoglycemia. For weight change, the only significant finding, reported by Hirao et al. (2008), was a greater increase in BMI associated with insulin aspart 70/30 than with a rapid-acting insulin analogue plus an intermediate-acting human insulin.[62] Over this study's 6-month treatment period, the mean change in BMI in the premixed analogue group was 1.47 kg/m^2 greater than the 0.8 kg/m^2 increase observed in the combined regimen group (P=0.013).

Premixed Insulin Analogues Versus Noninsulin Antidiabetic Agents

For minor hypoglycemia, a pooled analysis of 7 studies indicated that premixed insulin aspart 70/30 was associated with a greater risk than noninsulin antidiabetic agents (OR=3.8; 95% CI=1.7 to 8.5; P=0.001); the strength of evidence was determined to be high. In studies comparing insulin lispro 75/25 with noninsulin antidiabetic agents, inconsistent findings were reported for hypoglycemic events. In 1 study, rates of hypoglycemia were higher in the insulin lispro 75/25 arm (44.7% of patients) than in the glibenclamide arm (10.3% of patients; P=0.001).[56] In contrast, another study reported a trend in which the rate of overall hypoglycemia was greater among patients treated with glibenclamide than with insulin lispro 75/25 (P=0.07).[57]

Moderately strong evidence from 5 studies indicated that patients treated with insulin aspart 70/30 gained more weight than patients treated with noninsulin antidiabetic agents (mean difference=2.8 kg; 95% CI=0.6 to 5.0 kg; P=0.01). A similar finding associating greater weight gain with a premixed analogue was observed in the pooled analysis of studies on insulin lispro 75/25 (mean difference=1.88 kg; 95% CI=1.35 to 2.41 kg; P<0.001).

Take-Home Messages: Premixed Insulin Analogues Versus Noninsulin Antidiabetic Drugs

For lowering fasting glucose, postprandial glucose, and A1c, premixed insulin analogues are more effective than noninsulin antidiabetic drugs (●●).

However, noninsulin antidiabetic drugs are associated with lower rates of hypoglycemia (●●●) and less weight gain (●●).

●●=Moderate strength of evidence
●●●=High strength of evidence

Comparisons Among Premixed Insulin Analogues

Rates of hypoglycemic events generally did not differ in studies that compared one premixed insulin analogue to another. In a study conducted by Hermansen et al. (2002), hypoglycemia episodes occurred in 2 patients treated with insulin aspart 70/30 and 5 patients treated with insulin lispro 75/25.[37] Niskanen et al. (2004) reported similar rates of minor hypoglycemic events with insulin aspart 70/30 (43.2% of patients) and insulin lispro 75/25 (40.2%).[59] Crossover study designs prohibited analysis of weight changes in patients treated with different premixed analogues.

Clinical Outcomes

In the conceptual model that guided their systematic review, Qayyum et al. distinguished intermediate outcomes—fasting glucose, postprandial glucose, and A1c—from clinical outcomes. The latter encompasses the microvascular and macrovascular complications of type 2 diabetes as well as mortality. Regarding the comparative effectiveness of premixed insulin analogues on these clinical outcomes, Qayyum et al. were unable to draw firm conclusions due to major shortcomings in the existing literature. Nearly two-thirds of the studies included in the systematic review did not report the effects of premixed insulin analogues and other diabetes therapies on any clinical outcome. Those studies that did investigate these outcomes were limited by insufficient evidence; given the characteristically short duration of the studies, too few adverse clinical events occurred to enable sufficiently powered statistical analyses.

In comparisons of clinical outcomes among patients treated with premixed insulin analogues versus other therapies, there were no statistically significant differences in all-cause mortality, cardiovascular mortality, cardiovascular morbidity, or the combined outcome of all-cause mortality and cardiovascular morbidity. Across all studies reporting mortality outcomes, the percentages of patient deaths were generally similar in the premixed analogue and comparator arms. However, the number of deaths was typically low. Even in the longest study included in the systematic review, which followed patients for 2 years, few mortality events occurred.[34] This study, comparing insulin aspart 70/30 to NPH/regular 70/30, reported 1 death due to myocardial infarction in the premixed insulin analogue group versus no cardiovascular deaths in the premixed human insulin group. However, pooled analyses of 6 randomized controlled trials did reveal a trend of greater risk of all-cause mortality in patients treated with premixed analogues versus all other comparators combined (OR=2.93; 95% CI=0.95 to 9.05; P=0.06). Similarly, a trend associating premixed analogues with greater risk of cardiovascular death was observed (OR=6.80; 95% CI=0.87 to 53.12; P=0.07).

Qayyum et al. did not identify any study investigating the clinical outcomes of neuropathy or retinopathy in patients

treated with premixed analogues versus other diabetes therapies. In a 1-year study that reported nephropathy as an outcome, plasma creatinine increased significantly in patients treated with premixed and rapid-acting insulin analogues (0.05 mg/dL in both arms); a smaller increase in plasma creatinine was observed among patients treated with a long-acting insulin analogue (*P* value not reported).[19]

Adherence and Quality of Life

Qayyum et al. found no evidence on patient adherence to premixed insulin analogues versus other insulin and noninsulin diabetes therapies. As a surrogate for adherence, the EPC researchers assessed quality of life outcomes. Six studies were identified that compared premixed analogues with other antidiabetic agents and assessed quality of life. With 1 exception, the EPC researchers found no significant differences in quality of life among patients receiving different diabetes therapies. In a randomized controlled trial that used a validated questionnaire for assessing various quality of life measures, psychological distress scores were lower in patients treated with insulin aspart 70/30 versus oral antidiabetic agents (P=0.026; no quantitative measures of psychological stress were reported).[53] Due to inconsistencies in the definitions and measurements of quality of life across studies, Qayyum et al. were unable to draw firm conclusions for this outcome.

Effectiveness and Safety of Premixed Insulin Analogues in Subpopulations

As introduced earlier, the third Key Question that motivated the AHRQ systematic review involved potential differences in outcomes across subpopulations, including the elderly, males and females, racial groups, and individuals with comorbid medical conditions. In their literature search, Qayyum et al. found no studies that were specifically designed to directly compare outcomes between these subpopulations and the general population of people with type 2 diabetes. One study comparing insulin lispro 75/25 with glyburide included a distinctly older population of patients between 60 to 80 years old.[58] The results for this group indicated advantages of insulin lispro 75/25 for lowering fasting glucose (mean difference=−43.9 mg/dL; P<0.01), postprandial glucose after breakfast (mean difference=−58.3 mg/dL; P<0.01), and A1c (mean difference=−0.78%; P<0.01).

Premixed Insulin Analogue Monotherapy Versus Combined Therapy with Oral Antidiabetic Agents

The fourth Key Question that motivated the AHRQ systematic review focused on the effectiveness and safety of premixed insulin analogues in people who were also receiving treatment with oral antidiabetic agents. In addition, this question addressed the effects of premixed analogues in people with different blood glucose patterns (e.g., fasting hyperglycemia or postprandial hyperglycemia) or intensities of blood glucose control (e.g., tight control, usual control, good fasting, or postprandial control).

Qayyum et al. found 3 published studies comparing premixed analogue monotherapy to combined therapy with oral antidiabetic agents.[49,51,53] In these studies, insulin aspart 70/30 was compared with a combination of either insulin aspart 70/30 plus metformin[51,53] or pioglitazone.[49] In all 3 studies, decreases in fasting glucose concentrations were greater in patients receiving combination therapy with an oral antidiabetic agent versus premixed analogue monotherapy; however, the differences were not statistically significant. Reductions in postprandial glucose also favored combination therapy, but the differences were significant in only 1 of the 3 studies.[53] In all 3 studies, A1c reductions were significantly greater in patients receiving combination therapy versus premixed analogue monotherapy (pooled mean difference=0.37%; 95% CI=0.12% to 0.62%; P=0.004).

For minor and symptom-only hypoglycemia, pooled analyses indicated no difference between insulin aspart 70/30 monotherapy and combination therapy with an oral antidiabetic agent.[49,51,53] Similarly, no significant differences in weight change were observed between the monotherapy and combined therapy arms in the 3 studies.

Qayyum et al. did not identify any trials designed to investigate the effects of premixed insulin analogues in patients with different glycemic patterns or intensities of glycemic control.

Study Limitations and Implications for Clinical Applications

As recognized by Qayyum et al. in their AHRQ report[10] and in a review published in the *Annals of Internal Medicine*,[63] methodological issues may have compromised the precision and generalizability of some of their findings. A number of these issues are inherent to the studies on which the systematic review was based. A case in point involves the results indicating that premixed insulin analogues were more effective than premixed human insulin in lowering postprandial glucose. As noted by Qayyum et al., in many of the studies that made this comparison, the premixed human insulin was administered late (<30 minutes before meals), which could have reduced its effectiveness.[63]

The authors also note studies that did not control for between-group differences in total daily insulin dose. As explained earlier, in some studies therapy doses for individual patients were adjusted to optimize glycemic control. A fairly common outcome of these studies was a difference in the total daily insulin dose between patients treated with a premixed analogue versus a comparator insulin therapy. For example, in several studies comparing premixed analogues to long-acting analogues, the total insulin dose was significantly higher in the premixed analogue arms.[20-26,29] In these studies, premixed

analogues were more effective than long-acting analogues in lowering A1c. As Qayyum et al. suggest, this finding may have been influenced by the higher insulin dose of the premixed analogues (as opposed to their unique pharmacokinetic properties).[63]

The studies included in the AHRQ systematic review generally represented the United States population with respect to age, sex, and other demographic factors. However, most of the studies were clinical trials designed to demonstrate efficacy (whether a therapy can produce a narrowly defined effect in a research setting) rather than effectiveness (whether a therapy improves disease conditions in real-world settings). The efficacy trials thus excluded patients with diabetes-related complications and comorbidities. In addition, the follow-up periods of these trials were relatively short. Thus, applications of the AHRQ systematic review findings depend on assumptions about their generalizability to the larger population of individuals with type 2 diabetes over long durations.

Conclusions and Future Directions

The primary goal of this *JMCP* supplement series is to summarize the evidence presented in AHRQ's full comparative effectiveness report on premixed insulin analogues, which was published in 2008.[10] Of course, research on the comparative effectiveness and safety of diabetes therapies is constantly evolving, as are their roles in clinical practice. The evidence derived from the AHRQ systematic review indicates that the comparative effectiveness of premixed insulin analogues varies by specific comparator therapies and measures of glycemic control (Table 2). Thus, as emphasized in this article's clinical reflections, appropriate applications of the findings to making treatment decisions depend on individual patient circumstances. Moreover, the systematic review indicates tradeoffs between benefits and harms, especially when premixed insulin analogues are compared with long-acting insulin analogues and noninsulin antidiabetic drugs. In clinical applications, a balance must be achieved between optimal glycemic control and the adverse effects of hypoglycemia and weight gain.

Among its other unique advantages for advancing health care knowledge and clinical practice, comparative effectiveness research brings to light gaps in the published literature on treatment alternatives. The systematic review process naturally engenders progressive ideas for future research. In concluding their report on premixed insulin analogues, Qayyum and coworkers provide an extensive list of research directions (see reference 10, pages 97 and 98). In summary, the authors suggest new studies be conducted on premixed insulin analogues to determine whether their comparative effects (a) are sustainable over long periods of time; (b) apply in real-world settings, among patients with diabetes-related comorbidities and complications; and (c) apply to special populations, including the elderly and racial minority groups. In addition, Qayyum et al. call for new studies focused on the most relevant clinical outcomes, including cardiovascular morbidity and mortality, as well as outcomes of adherence and quality of life.

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